Diuretic Drugs

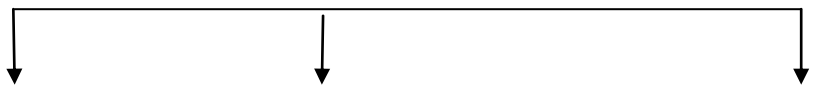
Main points:

1. The physiology of the nephron. It's important in drug action and responses.
2. Main classification of diuretic drugs → There's five classes. → /in each class:
3. Site of action (where they act)
4. Pharmaceutical effect: a) Desired effect. b) Undesired effect (side effect)
5. Clinical uses.
6. Contraindication and promotion. When I can use it and when I can't use it.

Concept of diuretics:

Diuretic in general are drugs that used to decrease the volume overload in the body (like in):

1. Edema
2. Hypertension (Na+ increase)
3. Electrolyte disturbances.



Hypocalcemia(K+) hypocalcemia (Ca+) Hypernatremia (Na+)

These are three important disorders for diuretics: A.H.T (Edema and Electrolyte disturbances).

- These drugs increase the volume of urine and the rate of urine formation.
- These drugs act from the luminal site of the nephron. Not all the diuretics act from the luminal site but most of them except spironolactone which acts from basolateral site (blood cell).
- They should present in urine → that mean the concentration in urine is important .
- Take the drug orally or I.V → Absorbed → Distributed → Then continuous in the urine and give the action.So any drug that decrease the GFR will decrease the concentration in urine and will decrease the diuretics effect like:
    - ➔ Hypertension (decrease filtration) but they are filtrate and also secreted from the tubular cells
    - ➔ That mean they have 2 ways to enter the lumen:
        1. Filtration
        2. Secretion

In renal failure when we use Furenmide, there is no filtration but there is another way to enter the lumen by the secretion.So it is use in acute and chronic renal failure B/C it is a Diuretic that increase the urine formation and help the patient B/C it is secreted from the tubular into the lumen.So they are useful in edema like CHF, Cirrhosis and Nephrotic syndrome.These two conditions, cirrhosis and Nephrotic syndrome we have hyperaldosteronism (high aldosterone in the blood).

<u>What is the effect of Aldosetrone?</u>

Increase reabsorption of Na+ (Expansion of the fluids) and increase Excretion of K+ (Hypokalemia)So the patient in cirrhosis or nephrotic syndrome does not need increase Na+. we give diuretic which blocks the aldosetrone action like spironolactone → the drug which use in cirrhotic edema and nephrotic edema.

Main physiology of the nephron:

First segment: it is composed of different segments:

Proximal tubules → Tubular cell → Basolateral extracellular and then come connection with blood.

This is important cells for absorption from the lumen into the tubular cells into the extracellular.

Second segment: Descending loop and ascending loop and then we have the distal tubules.

These different segments have different physiological function for example in proximal tubules the reabsorption of electrolytes, the same and water is Isotonic (same number of electrolyte, same with water).
Then the electrolytes pass to the descending loops (Here only the reabsorption of water) This site is passive for water, so the water here is reabsorbed and enter the ascending loop and become hypertonic.
So the ascending loop of Henle's contains hypertonic urine that concentrate Na, K, and so on.Here is an enzyme or a transporter which called Na/ K2 Cl transporter. This transporter takes the fluids (electrolytes) from the ascending loop again into the blood (reabsorption)
And they are only 20% of all solute NaCl is reabsorbed.
How will become the urine? Dilutive urine B/C it absorbed the electrolytes(enter of Na, K, Ca) and Na enter for fluids → The permeability for electrolytes: no permeability for fluids (water) . so it forms Dilutive urine.

> **The Distal part:** The first early part is called (Dilutive segment) B/C it contains dilutive urine.

Note: Dilutive segment or early distal tubule are the same.These reabsorption of Na in this site is for reabsorption of 10% of the remaining of solute. So we have 60% reabsorption, 25% reabsorption of electrolytes and have only 10%. That means the function of the distal loop is moderate (not strong), it is strong in the loop of Henle's B/C No more of the electrolyte, 25% Here is only isotonic of the beginning
Thiazide acts mainly in the early distal tubules where is the function is moderates, so
<u>what is the action of thiazide moderate or high?</u>
The action of thiazide moderate, it is a diuretic decrease the reabsorption of Na. then the filtrated urine passes to the late distal tubules. In the late distal tubules, we have 2 types of transporter that transport again the electrolytes into the extracellular and back to the blood.So we have sodium in and potassium out this is the first transporter. The second transporter is sodium in and proton out. In this site is the function of aldosterone.

Sites of the function of aldosterone in the nephron:

1. Distal tubules.
2. Collecting ducts.

<u>So what's the function of aldosterone?</u>

- ➔ Binds to the receptors in the basolateral site and lead to activation of these receptors to produce protein, this protein opens the Na channel so that allow the entrance of Na, K as an electrolytes)
- ➔ The function of aldosterone is to increase K secretion and Na reabsorption.In the collecting duct now we have the urine and should be concluded.

How much urine in the late tubules? 1.5 letter/ day. so to conclude the urine the remaining of the water should be reabsorbed and this is the function of vasopressin. so what's the function of vasopressin → binds to the receptors and lead to production and opening of specific protein which called Aquaporin.
Aquaporin: is a water channel-when it is opened, The water enters and then we have concentrated the urine.

There is a patient who has inactive vasopressin and we called it Antidiuretic hormone ADH. When we have low activity of vasopressin , so here the water not reabsorbed B/C the urine is durative and we called this condition → Diabetes inspidus)
Diabetes insipidus is a condition where a vasopressin is inactive and can lead to decrease the reabsorption of water.

The classification of diuretics drugs:

As mentioned, we have 5 groups,

The first group: is called carbonic Anhydrase inhibitor:
What is carbonic anhydrase inhibitor?
For example, we have drug which called acetazolamide, also called Diamox and use for eye for glaucoma.
<u>The site of action:</u> proximal tubules PT
<u>Mechanism of action:</u> inhibit the enzyme which called carbonic anhydrase. Carbonic anhydrose is an enzyme distributed all over the body, if present in the eye cell in the blood, in GIT to facilitate the reabsorption of bicarbonate.

Mainly in the nephron will see, we have filtrate and bicarbonate is filtered like HCO3
How reabsorption should occur? The cellular reabsorption should occur by the help of carbonic Anhydrase (this bicarbonate with proton come from the tubular cell and from carbonic acid.The carbonic acid (HCo3) dissociate and give CO2 + water. CO2 is a gas, this gas is diffused again to tubular cells and under the effect of this enzyme the CO2

binds again with water and forming again Bicarbonate and proton.The bicarbonate was in the lumen and convert to CO2.This gas diffuses to the tubular cells, in the tubular cell there's carbonic Anhydrase enzyme which convert CO2 to bicarbonate again.This bicarbonate is transported by active transport by basolateral, extracellular and then to the blood. Proton is important, it is secreted in the lumen (urine) so the acetazolamide will block the carbonic anhydrase intracellular and extracellular, that mean no reabsorption of bicarbonate.The bicarbonate secreted in the urine (alkaline urine). So the first side effect of this drug is alkaline urine.
Why alkaline urine? B/C no absorption of bicarbonate.
Alkaline is a medium for growth of bacteria and infection. And it is a medium for precipitation of some ions become renal stones, so , the using of this drug for long time if →infection and renal stones.

If the patient has cirrhosis or liver disease. this usually is sensitive to (Ammonia)and ammonia will be reabsorbed in alkaline urine.Again, the patient has cirrhosis and he use acetazolamide. So the urine become alkaline, the ammonia in this patient will reabsorbed again in the liver and enter the brain, so we have encephalopathy. B/C of alkaline urine and ammonia reabsorption (this is the first adverse effect of acetazolamide)

Second adverse effect: is a metabolic acidosis due to retention of proton to the blood. Then we have also disturbance in CNS due to disturbance in electrolytes.

What about levels of Na+ and k+ when we use acetazolamide?
Hyponatremia (decrease Na+) and Hypokalemia (decrease K+) B/C the absorption of Na+ occur when the Na+ is isotonic but when we use this drug acetazolamide which inhibit the bicarbonate so the Na+ will be hypertonic (not isotonic) so leads to disturbances in reabsorption of Na (some of Na not all Na) so leads to mild Hyponatremia and mild hypo kalmia

<u>So what is the use of this drug?</u>
It is not use as a diuretic→ why? It is use for glaucoma and motion sickness.

The physiology of nephron, if I block the proximal part, what happen? When I block the proximal loops by this drug will lead to increase the reabsorption in loop of Henle's?
So the effect of this drug is self limited.
So the acetazolamide not use as a diuretic. B/C we need to secrete the fluids and its function in proximal part. So if is not working as a diuretic B/C if leads to compensation.

So it uses only for glaucoma
In glaucoma there's formation of carbonic Anhydrase and lead to increase of lumen fluids (increase fluids under the eye).
So we should block carbonic Anhydrase and decrease and decrease intraocular pressureto the fluids.
Now the question is: acetazolamide is a diuretic or not?
Yes, B/C it acts on nephron.
Second question: is it used as a diuretic?
No, it is not used, so this drug is a diuretic but not used as a diuretic B/C its self limited effect 'side effect'.

Second group: loop diuretic:
We have 5 drugs in this group the main drug is furosemide (Lasix) and the other one: Torasemide(Bumetanide) other names in the hand out..
These five drugs are one potent loop diuretics.

Site of action: in the ascending loop of Henle's
MOA: inhibit Na+/K+_2Cl- transporter
We know the physiological function. It is a major function for electrolytes reabsorption.
So when we block it → the electrolytes not reabsorption and B/C it is massive , it will take a lot of fluids with it. So we have massive diuretic.
And this massive diuretic will go on and Of urine
So it is useful in cases of emergencies. Like:
High blood pressure → 180/100 give the patient I.V fursemide and we have increase outflow of urine → that means decrease Na+.
This the first mechanism it is Na+/K+ transporter. This transporter is present also in the macula densa. these macula densa cells have the same transporter. so fursemide will block the function of these cells.
What will be the results?Increase GFR, the macula densa make regulation and decrease GFR so, when I block it (block macula densa function). This will lead to increase GFR.
So the second action is: increase GFR → is it good for renal failure or not? Yes, it is good for any renal impairment or renal insufficiency B/C of increase GFR (in poisoning or Patient is going trauma).

Third action: decrease and block Ca+ reabsorption (decrease and block)
What is the effect? Hypocalcemia

So, it is useful with patient who is suffering of high level of calcium in blood (inhypercalcemia)
The main function of fursemide in the nephron:

1. Increase massive diuretic
2. Increase GFR
3. Increase secretion of Ca+.

And it is usually will taken mainly orally.

What about parenteral? (I.V)
Immediately it increases the production of prostaglandin that lead to vasodilatation and this leads to increase venous capacitance. That mean all blood go to the vein. So in pulmonary edema(congestive) it will improve this case by decrease the preload (يقلل من الدم الراجع) so it is used as a treatment of pulmonary edema. so again the immediate I.V injection of fursemide produce immediate vasodilatation and leads to because of prostaglandin .Leads to increase venous capacitance and decrease pulmonary edema in the patient has left ventricular failure or patient has sever edema and A.H.T.
These effect in the vessels (dilatation)By I.V injection is before entering the nephron (still in circulation). And when reach the nephron will do the another effect → massive diuretic ,it is taken parentrally but like the effect of oral rout.
So it is very active drug (given orally and parenterally).
N.B: the patient may suffer from dehydration so we don't use it in chronic cases (only in short cases and emergencies) for 2 weeks and if the situation need for one month.
Main side effect:

1. Hyponatremia (decrease Na+)
2. Hypokalemia (decrease K+)
3. Hypocalcemia (decrease Ca+
4. Hypomagnesemia (decrease Mg+)
5. Hyperurecemia
6. Hyperglycemia

Hyperuricemia: B/C furosemide is an acid and uric acid is an acid also. So, there's completion between fursemide and uric acid.
The furosemide must excrete but the uric acid prevents it.(there's competition)
There's high affinity of fursemide to carrier. So displace uric acid and uric acid return to the blood and leads to Hyperurecemia.

7. Metabolic Alkalosis:By inhibiting the Na+ re absorption in the ascending loop, the Na+.delivering to the distal tube will increase, this will lead to increase secretion of K+ and protons H+ but because There is Hyopkalemia so the discharge of protons H+ will be more increased lead to alkalosis.

what are the clinical uses of furosemide?

1. Edema 2. Hypertension 3. Renal failure 4. Hypocalcemia
   5. Hypocalcemia 6. Pulmonary edema 7. Nephrotic syndrome
   8. Cerebral edema and pre caution in dehydration.

Thiazide Diuretics:

1. Hydrochlorothiazide 2. Indapamide
   3.metlazone and so on…

Indapamide and Metalazone are more potent (more effective) Than hydrochlorothiazide. Hydrochlorothiazide clinical dose 25-50 mg

Site of action: Early distal tubules.
Mechanism of action:Inhibition of (Na+, K+, Mg+, CL-) re absorption
The characteristics of thiazide group are:

1. Moderate diuretics effect, because the physiological function of the early distal tubule is moderate.
2. Long action.
3. Used in the treatment of chronic hypotension.
4. Increase the Ca+ re absorption.

While Furosemides characteristics are:

1. Active and massive diuretics effect.
2. Short action
3. Drug of choice for ACUTE hypertension (emergency cases)
4. Decrease the re absorption of Ca+

How is the effect of Thiazide?

How does thiazide work as mild anti-hypertensive when patient take this drug? at the first day no change will occur in the blood pressure,but after one or two weeks the blood pressure will be decreased. why?

Because with continues loss of fluid, the GFR will be decreased, and this will have decreased the blood volume and the cardiac output.
All of this events will occur through the first two weeks. But after many weeks the Na+ will be low, so the vessels.
Sensitivity will be also low, this will decrease the vascular peripheral resistance, which mean decrease in the blood pressure, and the cardiac output will be returned to normal.

Thiazide maximum dose is 50 mg, not more than this, because any further increase in the dose will not make any increase in the effect.
But in case of furosemide any increase in the clinical dose, will increase the effect.
Patient with renal failure can be given 200mg fursemide, if there is no any improvement We can increase the dose 300 mg, 400 mg,600 mg because as we mentioned before (increase in furosemide dose, will increase the effect.
Side effects:

1. Hyponatremia
2. Hyopkalemia
3. Hypomagensia
4. Hypercalcemia, because the second action of thiazide is increase the reabsorption.That's why the thiazide is good for patient with osteoporosis and patient with calcium renal stone(calciurea).

Thiazide also used as drug of choice for diabetes inspidus. How?

1. by decreasing the GFR, due to continuous loss of fluids.
2. by activation in the production of the protein (Aquaporin), this protein increases the reabsorption of water.

The fourth group: Potassium – sparing diuretics
Diuretics which spare K+ in the blood, lead to hyperkalemia. there are two groups of potassium-sparing diuretics.

First group are steroids like structure examples of this group is spironolactone. Which is indirect acting drug.And because it has the same structure of steroid drugs, it has the same side effects of steroid drugs.

Second group is non- steroid like structure examples of this group is:
Triamterene _ Amiloride

They are direct acting drugs.

The second g3roup: site of action is: in the late distal tubules.

Mechanism of action:
They block the Na+ channels, so Na+ is not reabsorbed and this lead to hyperkalemia
These diuretics very weak in effect, so I can make combination of one of this drug with another drugs, because they have weak effect.
The main use of this group is to spare potassium, so I can combine them with thiazide and Furosemides to prevent the side effect of thiazide and furosemide (prevent Hypokalemia)
The first group:spironolactone which is indirect acting drug, it is aldosterone antagonist. That inhibit the action of aldosetrone by be binding to aldosetrone receptors, so Na+ channels are not open and this will decrease Na+ reabsorption and increase K+ return to the blood, lead to increase hyperkalemia andhyponatremia.
This mean that when we use diuretics that cause Hyopkalemia like, fursemide and thiazide, we give also potassium- sparing diuretics like spirolactone to balance the loss of potassium.

The main use of spironolactone:

- Balance K+ loss
- Can be used in primary and secondary hyper aldosetrone, like in case of cirrhotic edema, I will give fursemide to increase fluid loss, and also I will give the patient spiroactone to save the K+ and balance the loss.
- So spiroactone is used in combination with other drugs to block aldosetrone and spare the potassium.
- In congestive heart failure:
  In chronic second or third stage of CHF, high level of aldosterone will be in the blood (hyperaldosteronism)
  What is the role of aldosetrone in CHF?
    1. By increasing the Na+ reabsorption will lead to expansion of extracellular fluid and increase the preload, so we will use antagonist of aldosetrone (spiroactone) in order to decrease the preload to the heart.
    2. Increase fibroblast proliferation lead to fibrotic change and decrease in the systolic function.
    3. Activation of sympathetic system (adrenaline and Noradrenalin).

So, we need to block the aldosetrone receptors to prevent the effect of it.

Side effects of spironolactone:

- Hyperkalemia
- Hyponatremia
- And because it has steroid structure it will cause peptic ulcer, impotence, gynecomastia, hirsutism(increase in the hair growth)
  How does spironolactone cause hirsutism andgynecomastia?
  By acting on sexual Hormon receptors (Testerone + Estrogen hormones.